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Reduction of Nitroarenes to Anilines with a Benzothiazoline: Application to Enantioselective Synthesis of 2-Arylquinoline Derivatives

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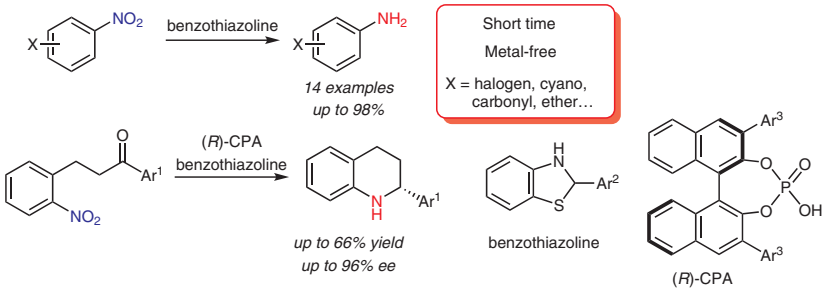

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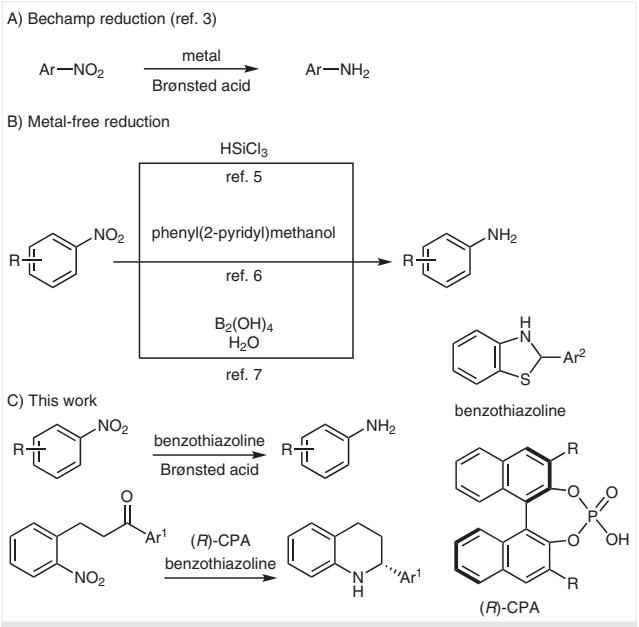
Abstract The metal-free reduction of nitroarenes to aniline derivatives was accomplished in a short time by using a benzothiazoline as the hydrogen donor in combination with a Brønsted acid. An enantioselective synthesis of 2-arylquinolines was achieved by using 1-aryl-3-(2-nitrophenyl)propan-1-ones as starting materials and a combination of a benzothiazoline and a chiral phosphoric acid.

Key words benzothiazolines, phosphoric acids, isoquinolines, nitroarenes, anilines, reduction

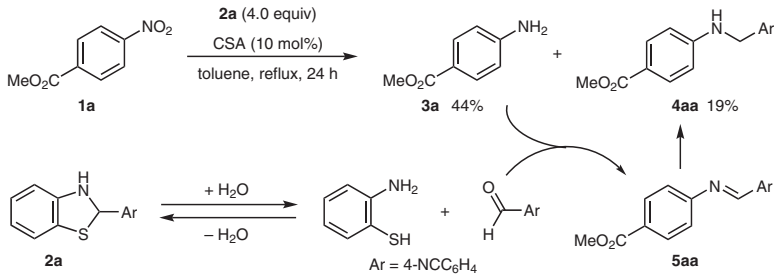
Aniline is a fundamental motif, frequently found in pharmaceuticals, natural compounds, and building blocks. It is also an important building block for organic synthesis.[1] A conventional method for the synthesis of aniline involves the reduction of aryl nitroarenes by using metals.[2] The Béchamp reduction, which uses tin or zinc in the presence of a Brønsted acid at high temperature, is extensively employed.[3] Alternatively, transition-metal-catalyzed reductions of nitroarenes with hydrogen gas are used under relatively mild reaction conditions. Palladium on carbon is a widely used catalyst in reductions performed in the laboratory and industry because it presents benefits with regards to cost and handling.[4] However, the reduction using palladium is sometimes hampered by such issues as residuals, flammability, and chemoselectivity. The reduction of nitroarenes by using such organic reductants as trichlorosilane[5] or phenyl(2-pyridyl)methanol[6] has been developed. Recently, Uozumi and co-workers reported a reduction that used diboronic acid and water.[7]

We have reported an enantioselective transfer hydrogenation of ketimines, in which we used a benzothiazoline (2,3-dihydro-1,3-benzothiazole) as the hydrogen donor in combination with a chiral phosphoric acid.[8,9] Benzothiazolines proved to be effective for the transfer hydrogenation of C=N bonds in a range of ketimines. To expand the utility of benzothiazolines, we set our sights on the reduction of nitroarenes. Here we describe a rapid metal-free reduction of nitroarenes that uses a combination of a benzothiazoline and a Brønsted acid. Furthermore, we applied this reaction to the enantioselective synthesis of 2-arylquinolines, starting from 1-aryl-3-(2-nitrophenyl)propan-1-ones (Scheme 1).



Scheme 1 Reduction of nitroarenes

At the outset, we examined the reduction of methyl 4-nitrobenzoate (**1a**) with 2-phenylbenzothiazoline (**2a**) in the presence of a catalytic amount of 10-camphorsulfonic

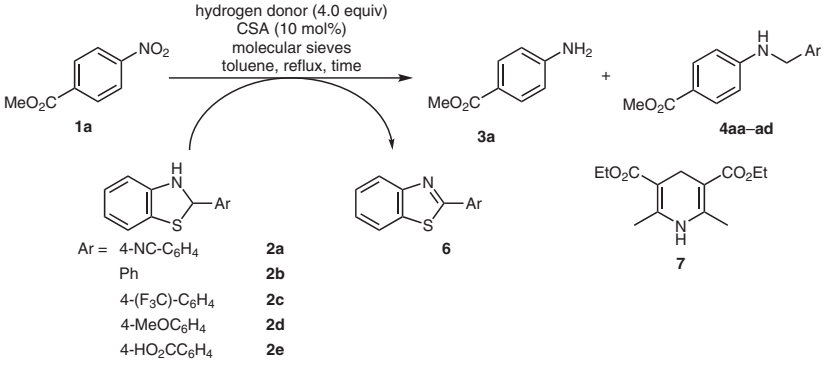


Scheme 2 Reduction of nitroarenes and the formation of *N*-benzylamine **4aa**

acid (CSA) as a Brønsted acid (Scheme 2). Gratifyingly, aniline **3a** was obtained in 44% yield, accompanied by the corresponding *N*-benzylamine **4aa** in 19% yield. We already knew that the hydrolysis and condensation of benzothiazolines and benzaldehydes occur under these reaction conditions. We therefore believed that **4aa** was formed by the reduction of imine **5aa**, derived from **3a** and 4-cyanobenzaldehyde.

In order to suppress the hydrolysis of the benzothiazoline **2a** and to increase the yield of **3a**, we added molecular sieves (MS), which had a pronounced effect; the addition of MS 4Å suppressed the formation of the benzylamine **4aa** and gave aniline **3a** in high yield (Table 1, entries 1–3). Next, we explored the effects of the Brønsted acid and of various 2-substituents on the benzothiazoline. A long reaction time was required in the absence of a Brønsted acid (entry 4). The 2-substituent on the benzothiazoline did not affect the yield (entries 5–7). During the investigations, we had difficulties purifying the aniline after the reaction, because an excess of benzothiazole **6** (Ar = Ph) was generated and the separation of the desired product **3a** from **6** (Ar = Ph) was not a trivial issue. We surmised that the introduction of a carboxy group onto the benzothiazoline **2** might increase its polarity and facilitate separation. In addition, we expect-

Table 1 Effects of Molecular Sieves and Various Substituents on the Benzothiazoline[a]

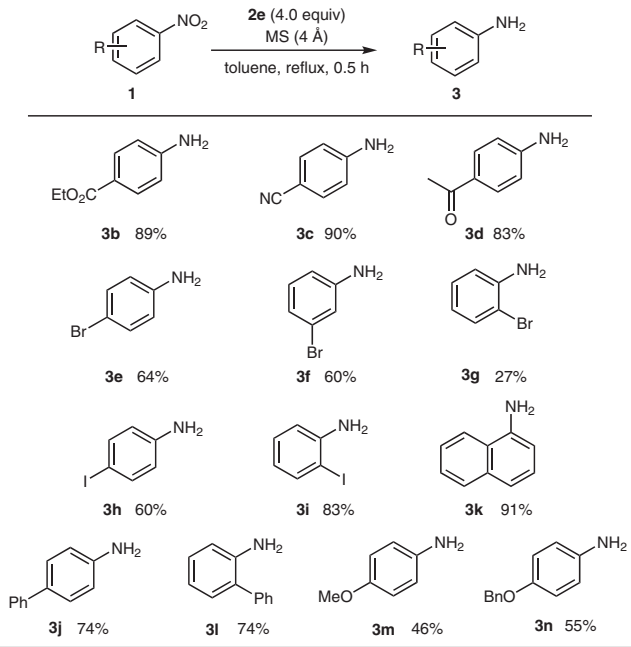


Entry	H donor	MS	Time (h)	Yield (%) of **3a**	Yield (%) of **4**
1	**2a**	MS 3Å	24	43	0
2	**2a**	MS 4Å	24	86	5
3	**2a**	MS 5Å	24	52	27
4[b]	**2a**	MS 4Å	48	88	<8
5	**2b**	MS 4Å	19	84	15
6	**2c**	MS 4Å	24	87	10
7	**2d**	MS 4Å	10.5	75	<38
8[b]	**2e**	MS 4Å	0.5	98	-
9	**2e**	MS 4Å	0.5	97	-
10	**7**	MS 4Å	20	23	-

[a] Reaction conditions: **1a** (0.080 mmol), H donor (0.32 mmol), CSA (0.008 mmol), MS (100 mg), toluene (0.80 mL).
[b] Without CSA.

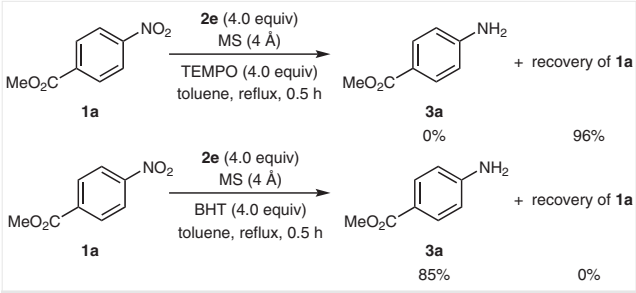
ed that the benzothiazoline bearing a carboxy group **2e** might function as a Brønsted acid instead of CSA. We therefore attempted to perform the reaction with **2e** in the absence of CSA (entries 8 and 9). As expected, benzothiazole **6e** was readily removed from the crude mixture by filtration with dichloromethane. Gratifyingly, the use of **2e** accelerated the reaction remarkably and improved the yield of **3a** to 98% in 0.5 hours. We also examined the utility of the Hantzsch ester (**7**) as a hydrogen donor in place of a benzothiazoline, but this gave **3a** in low yield (entry 10).[10] Benzothiazoline **2e** was therefore found to be the most suitable hydrogen donor for the present reduction.

Having clarified the optimal reaction conditions, we investigated the substrate scope. Nitroarenes bearing electron-withdrawing groups, such as an ester, nitrile, or ketone group, gave the desired anilines **3b–d** in excellent yields (Scheme 3). Bromo- and iodo(nitro)benzenes provided the corresponding anilines **3e–i** in good yields, except for 2-bromo-1-nitrobenzene. 4-Methoxy and 4-(benzyloxy)-1-nitrobenzenes gave the desired anilines **3m** and **3n** in moderate yields, because benzylamines **4ma** and **4na** were also formed. The reduction was completed in 0.5 hours for all substrates. Aliphatic nitro compounds, nitrobenzenes bearing vinyl groups, and *trans*-β-nitrostyrene were not suitable substrates for this reduction, and the corresponding anilines were not obtained.



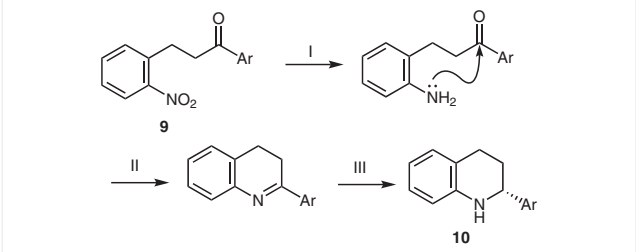
Scheme 3 Substrate scope of nitroarenes

We hypothesized that the reduction proceeds by a radical pathway. 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added to the reaction mixture as radical scavengers. The addition of TEMPO suppressed the reduction completely, and 96% of **1a** was recovered. On the other hand, amine **3a** was obtained in 85% yield when BHT was added (Scheme 4). The latter result did not agree with our hypothesis, so we are exploring other reaction pathways.



Scheme 4 Mechanistic study

The present reduction of nitroarenes was applied in a tandem reaction to synthesize 2-substituted chiral quinoline derivatives (Scheme 5).[11] The tandem reaction consists of (I) reduction of a 1-aryl-3-(2-nitrophenyl)propan-1-one **9**, (II) imine formation by intramolecular cyclization, and (III) asymmetric reduction by a chiral phosphoric acid and a benzothiazoline.[12]



Scheme 5 Tandem reaction

We optimized the reaction conditions to furnish the desired 2-arylquinolines **10a–c** in good yields and with excellent enantioselectivities by the combined use of benzothiazoline **2f** and chiral phosphoric acid **8** (Scheme 6).[13]

In summary, we have developed a reduction of nitroarenes by using a benzothiazoline in the presence of a Brønsted acid. The reduction with a benzothiazoline bearing a carboxy group was completed in a short time. Selective reduction without use of metal reagents was achieved. A tandem reaction with a chiral phosphoric acid and a benzothiazoline gave 2-aryltetrahydroquinoline derivatives with excellent enantioselectivities.

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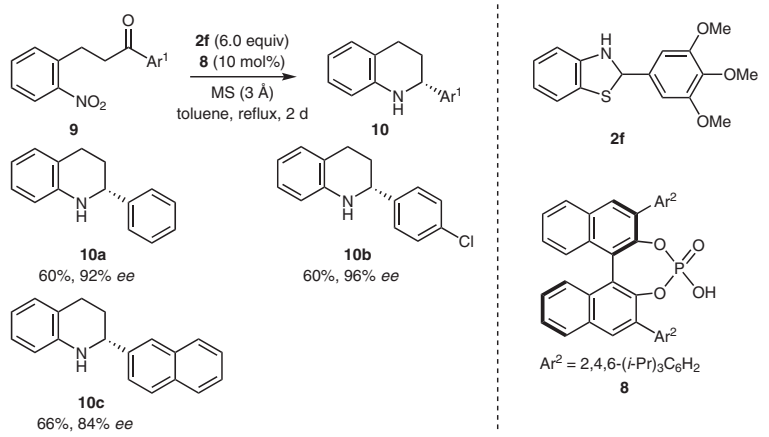

Scheme 6 Asymmetric synthesis of 2-substituted quinolines

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611639.

References and Notes

(1) (a) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121. (b) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, **2004**. (c) MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27.

(2) For reviews, see: (a) Kadam, H. K.; Tilve, S. G. *RSC Adv.* **2015**, *5*, 83391. (b) Blaser, H.-U.; Steiner, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210. (c) Orlandi, M.; Brenna, D.; Harms, R.; Jost, S.; Benaglia, M. *Org. Process Res. Dev.* **2018**, *22*, 430. (d) Aditya, T.; Pal, A.; Pal, T. *Chem. Commun.* **2015**, *51*, 9410.

(3) Béchamp, A. *Ann. Chim. Phys.* **1854**, *42[3]*, 186.

(4) Blaser, H.-U. *Chimia* **2015**, *69*, 393.

(5) (a) Porta, R.; Puglisi, A.; Colombo, G.; Rossi, S.; Benaglia, M. *Beilstein J. Org. Chem.* **2016**, *12*, 2614. (b) Orlandi, M.; Tosi, F.; Bonsignore, M.; Benaglia, M. *Org. Lett.* **2015**, *17*, 3941. (c) Orlandi, M.; Benaglia, M.; Tosi, F.; Annunziata, R.; Cozzi, F. *J. Org. Chem.* **2016**, *81*, 3037.

(6) Giomi, D.; Alfini, R.; Brandi, A. *Tetrahedron* **2011**, *67*, 167.

(7) Chen, D.; Zhou, Y.; Zhou, H.; Liu, S.; Liu, Q.; Zhang, K.; Uozumi, Y. *Synlett* **2018**, *29*, 1765.

(8) (a) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180. (b) Zhu, C.; Saito, K.; Yamanaka, M.; Akiyama, T. *Acc. Chem. Res.* **2015**, *48*, 388. (c) Zhu, C.; Akiyama, T. *Synlett* **2011**, 1251.

(9) For seminal papers on chiral phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. For selected reviews, see: (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Synthesis* **2010**, 1929. (e) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (f) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2017**, *117*, 10608. (g) Merad, J.; Lalli, G.; Bernadat, G.; Maur, J.; Masson, G. *Chem. Eur. J.* **2018**, *24*, 3925.

(10) For pioneering works on chiral phosphoric acid-catalyzed transfer hydrogenation of ketimines by using the Hantzsch ester as a hydrogen donor, see: (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (b) Hoffmann, S.; Seayad, A.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84; For selected reviews, see. (d) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852. (e) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498.

(11) For an enantioselective metal-free cascade reaction with a chiral phosphoric acid, see: Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683.

(12) Shibata, Y.; Yamanaka, M. *J. Org. Chem.* **2013**, For a theoretical study on chiral phosphoric acid-catalyzed transfer hydrogenation using a benzothiazoline, see: *78*, 3731.

(13) **2-Aryl-1,2,3,4-tetrahydroquinolines 10a–c; General Procedure**

Under a N_2 atmosphere, a mixture of the appropriate ketone **9** (0.10 mmol), benzothiazoline **2f** (0.60 mmol), chiral phosphoric acid **8** (0.010 mmol), and MS 3Å (600 wt%, activated) in toluene (1.0 mL) was refluxed for 2 days. When the reaction was complete (TLC), it was quenched by adding sat. aq $NaHCO_3$. The crude mixture was filtered through a Celite pad and extracted with EtOAc (×3). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC.

2-Phenyl-1,2,3,4-tetrahydroquinoline (10a)

White solid; yield: 13 mg (60%, 92% ee); mp 52–54 °C; $[\alpha]_D^{24}$ –42 (*c* 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.05 (m, 1 H), 2.09–2.15 (m, 1 H), 2.74 (dt, *J* = 4.8, 16.4 Hz, 1 H), 2.93 (ddd, *J* = 5.6, 10.8, 16.4 Hz, 1 H), 4.04 (br s, 1 H), 4.43 (dd, *J* = 3.4, 9.2 Hz, 1 H), 6.53 (d, *J* = 8.4 Hz, 1 H), 6.65 (t, *J* = 7.6 Hz, 1 H), 6.99–7.02 (m, 2 H), 7.24–7.40 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4, 31.0, 56.3, 114.0, 117.2, 120.9, 126.6, 126.9, 127.5, 128.6, 129.3, 144.7, 144.8.